US-PAT-NO: 6645506
DOCUMENT-IDENTIFIER: US 6645506 B1

TITLE: Topical compositions containing extracellular products of Pseudomonas lindbergii and Emu oil

DATE-ISSUED: November 11, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Farmer; Sean	La Jolla	CA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Ganeden Biotech, Inc.	San Diego	CA			02

APPL-NO: 09/ 383975 [PALM]
DATE FILED: August 26, 1999

PARENT-CASE:
RELATED APPLICATIONS The present application is a continuation-in-part (CIP) of, and claims priority to PCT Patent Ser. No. PCT/US98/07307, entitled: "TOPICAL USE OF PROBIOTIC BACILLUS SPORES TO PREVENT OR CONTROL MICROBIAL INFECTIONS", filed Apr. 10, 1998 and U.S. Provisional Patent Application Ser. No. 60/044,643, entitled: "TOPICAL USE OF PROBIOTIC BACILLUS SPORES TO PREVENT OR CONTROL MICROBIAL INFECTIONS", filed Apr. 18, 1997.

INT-CL: [07] A61 K 39/108, A61 K 39/07, A61 K 6/00, A61 K 35/00, A01 N 25/34

US-CL-ISSUED: 424/260.1; 424/431, 424/404, 424/246.1, 424/93.46, 424/401, 424/402, 424/115, 424/522, 424/78.05, 424/78.02, 435/252.3
US-CL-CURRENT: 424/260.1; 424/115, 424/246.1, 424/401, 424/402, 424/404, 424/431, 424/522, 424/78.02, 424/78.05, 424/93.46, 435/252.3

FIELD-OF-SEARCH: 424/431, 424/404, 424/260.1, 424/93.46, 424/401, 424/115, 424/402, 424/246.1, 424/522, 424/78.05, 424/78.02, 435/253.3

PRIOR-ART-DISCLOSED:

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Search Selected | Search ALL | Clear

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ART-UNIT: 1645

PRIMARY-EXAMINER: Minnifield; Nita

ATTY-AGENT-FIRM: Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C.

ABSTRACT:

The present invention discloses compositions derived from an isolated Bacillus species, spores, or an extracellular product of Bacillus coagulans comprising a supernatant or filtrate of a culture of said Bacillus coagulans strain, suitable for topical application to the skin or mucosal membranes of a mammal, which are utilized to inhibit the growth of bacterium, yeast, fungi, virus, and combinations thereof. The present invention also discloses methods of treatment and therapeutic systems for inhibiting the growth of bacterium, yeast, fungi, virus, and combinations thereof, by topical application of therapeutic compositions which are comprised, in part, of isolated Bacillus species, spores, or an extracellular product of Bacillus coagulans comprising a supernatant or filtrate of a culture of said Bacillus coagulans strain. In addition, the present invention also discloses compositions, methods of treatment, and therapeutic systems for inhibiting the growth of bacterium, yeast, fungi, virus, and combinations thereof, comprising an extracellular product of Pseudomonas lindbergii comprising a supernatant or filtrate of a culture of said Pseudomonas lindbergii strain.

23 Claims, 13 Drawing figures

WEST Search History

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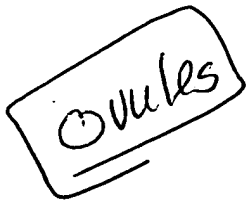

DATE: Tuesday, June 21, 2005

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		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=AND	
☐	L1	penal same vaccin$	0
☐	L2	penal.clm. same vaccin$.clm.	0
☐	L3	penal.clm. same implant$.clm.	0
☐	L4	penil.clm. same implant$.clm.	1
☐	L5	penile.clm. same implant$.clm.	162
☐	L6	penile.clm. same supposit$.clm.	2
☐	L7	L5 and ($suppository or supposit$)	2
☐	L8	l7 and (tween or polysorbate or poly-sorbate or polysorbate$ or $tween or tween$)	2
☐	L9	l7 and (tween or polysorbate or poly-sorbate or polysorbate$ or tween$)	0
☐	L10	penile or urogenital$ or genitourinary or genito-urinary$ or uro-genital or urino-genital or urinogenital$	13665
☐	L11	L10 and ($suppositories or $suppository or supposit$)	3611
☐	L12	L10 same ($suppositories or $suppository or supposit$)	132
☐	L13	l1 and (tween or polysorbate or poly-sorbate$ or polysorbate$ or tween$)	0
☐	L14	l1 and peg$	0
☐	L15	l11 and (tween or polysorbate or poly-sorbate$ or polysorbate$ or tween$)	1565
☐	L16	l12 and (tween or polysorbate or poly-sorbate$ or polysorbate$ or tween$)	54
☐	L17	(L16 or l15) and (polyethyleneglycol or peg or pegalate or peylate or peylation or pagylating or pegged or poly-ethylene-glycol or polyol or polyene or (polymer near5 glycol))	1054
☐	L18	l17 and vaccin$	603
☐	L19	l17 and (humoral$ or immune or immunity)	818
☐	L20	l16 and vaccin$	9
☐	L21	(l11 or l12) and (tween$ or polysorbate$ or poly-sorbate$ or $sorbate)	1583
☐	L22	L21 and (peg or polyethylene or poly-ethylene or glycol or polyethyleneglycol or pegconjugate or peg$ or ethyleneglycol or ethylene-glycol or pegylate or pegylation or gegged or pegylate or (polymer near5 glycol))	1525
☐	L23	antigen or antigenic or virus or viral or microbe or microbial or pathogen or rna or dsdna or ds-dna or cdna or mrna or immunogen or vaccine or bacteria or bacterial or humoral or uropathogen or uro-pathogen or vaccine or vaccination or immunization or immunising or immunisation	611617
☐	L24	L23 or hiv or parasite or parsitic	635897

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☐	L26	L25 and l12	37
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☐	L29	L28 same l24	3622
☐	L30	L28.ti,ab,clm. and l24	1726
☐	L31	L30 and l10	133
☐	L32	(peg or polyethylene or poly-ethylene or glycol or polyethyleneglycol or pegconjugate or peg$ or ethyleneglycol or ethylene-glycol or pegylate or pegylation or gegged or pegylate or (polymer near5 glycol))	1082222
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☐	L34	L33 and l32	62476
☐	L35	L33 same l32	27965
☐	L36	(L35 or l34) and (l29 or l30)	1221
☐	L37	L36 and l23	1212
☐	L38	l29 and l34	990
☐	L39	l29 and l35	178
☐	L40	L39 and l28 and l10	20
☐	L41	l10.ti,ab,clm. and l23.ti,ab,clm. and l32.ti,ab,clm. and l33.ti,ab,clm.	3

END OF SEARCH HISTORY

genitourinary

<anatomy> Pertaining to the genital and urinary organs, urogenital, urinosexual.

(18 Nov 1997)

Previous: genitocrural nerve, genitofemoral, genitofemoral nerve, genitoinguinal ligament
Next: genitourinary apparatus, genitourinary fistula, genitourinary system

genitourinary (GU) (jen'i-tō-ū'ri-nar-ē)

Relating to the organs of reproduction and urination. Syn: urinogenital, urogenital, urinosexual

Prev

DOCUMENT-IDENTIFIER: US 6159174 A
TITLE: Method of using lectins for therapy of diseases transmittable by sexual contact

Brief Summary Text (8):
Administration of biologically active materials to the vagina for whatever purpose is usually accomplished by the use of some device that provides for convenient application of the medication by the user herself. A variety of devices exist for delivery of bioactive substances such as spermatocides and various medications. Each has its place in the medical armamentarium but each has certain deficiencies for application of contraceptive or anti-microbial agents in the context of sexual activity. Conventional vaginal suppositories and ovules may not provide medication to the entire vagina because of their shape and placement by the user in the vagina. Such suppositories are generally comprised of a material that melts at body temperature to allow the medication to spread and contact the tissues. However, when the dosage form melts, the medication may drain out of the vagina rather quickly, thus minimizing its potential effectiveness and significantly reducing the extended exposure of the tissues and pathogens to the medication which is often necessary for effective treatment. Similarly, the effective duration of contraceptives applied in this way tends to be relatively brief. In addition, such delivery vehicles, even when freshly applied, do not provide any physical barrier to deposition of male ejaculate on the cervix. Such ready access of sperm to the cervix may allow them to escape the action of spermatocides that are diffused throughout the vagina. Furthermore, because cells at the cervix are uniquely sensitive to several pathogens such as Chlamydia trachomatis, the absence of a barrier deprives these cells of a significant means of protection.

Detailed Description Text (21):
The lectins may be administered in any fluid or ointment vehicle suitable for topical administration of pharmaceutical compounds. Thus creams, ointments, foams, suppositories, liposomes, ovules and the like may be formulated in which the selected lectins are dispersed in a non-toxic vehicle suitable for topical and in particular for vaginal administration. Such vehicles include oil-in-water and water-in-oil emulsions, white petrolatum, hydrophilic petrolatum, lanolin emulsions, polyethylene glycols, cocoa butter and the like. Useful vehicles include emollient oils such as water-soluble oils, e.g., liquid polyethylene glycols, which promote complete and uniform distribution of the medicament within the vagina. Representative suitable vehicles include a lubricating jelly comprised of water, propylene glycol, hydroxyethyl cellulose, benzoic acid and sodium hydroxide, a water-soluble oil comprised of water, glycerin, propylene glycol, polyquaternium #5, methyl paraben and propyl paraben; a cream comprised of benzyl alcohol, cetearyl alcohol, cetyl esters wax, octyldodecanol, polysorbate 60, purified water, and sorbitan monostearate; and a suppository comprised of polyethylene glycol (PEG) 18, PEG-32, PEG-20 stearate, benzethonium chloride, methyl paraben and lactic acid. The lectins can also be incorporated into any conventional controlled release system for releasing them gradually or in a controlled timed release profile to the site of intended activity. Such systems are well-known to those skilled in the art and include particles having coatings that dissolve or erode at different controlled rates in a body fluid, matrices, e.g., polymers from which the lectins can diffuse, erodible matrices that release lectins to the site of intended activity, or the like.

Detailed Description Text (26):
Thus the lectins to be introduced into the vagina can be incorporated in any conventional vaginal medication-dispensing device such as suppositories, ovules, pessaries and the like, including controlled-release systems as discussed above. The lectins may also be incorporated into conventional contraceptive devices such as diaphragms, cervical caps, vaginal sponges or the like. The lectins may be incorporated into the body of such devices or coated on the surface thereof, either neat or in a vehicle, e.g., as a dusting powder, or in a binder that provides a coating from which the lectins are released over a period of time. It is not excluded that the lectins may be bound covalently to the surface of the device.

CLAIMS:

13. The method of claim 1 wherein said site of infection is the female or male urogenital tract.

US006159174A

United States Patent [19]

Oldham et al.

[11] Patent Number: 6,159,174

[45] Date of Patent: *Dec. 12, 2000

[54] METHOD OF USING LECTINS FOR THERAPY OF DISEASES TRANSMITTABLE BY SEXUAL CONTACT

[75] Inventors: **Michael J. Oldham**, Ventura, Calif.; **Bruce F. Rose**; **Howard C. Krivan**, both of Carson City, Nev.

[73] Assignee: **Legere Pharmaceuticals, Ltd.**, Carson City, Nev.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **09/199,045**

[22] Filed: **Nov. 24, 1998**

Related U.S. Application Data

[63] Continuation-in-part of application No. 08/938,831, Sep. 26, 1997, Pat. No. 5,840,771, which is a continuation of application No. 08/759,517, Dec. 4, 1996, abandoned, which is a continuation of application No. 08/609,104, Feb. 29, 1996, abandoned, which is a continuation of application No. 08/462,666, Jun. 5, 1995, abandoned, which is a division of application No. 08/317,599, Oct. 3, 1994, abandoned, which is a continuation-in-part of application No. 08/130,190, Oct. 1, 1993, abandoned.

[51] **Int. Cl.**[7] **A61L 15/00**

[52] **U.S. Cl.** **602/77**; 604/48; 604/500; 604/514; 604/515; 604/518; 604/346; 514/931; 514/933; 514/934; 514/967; 424/195.1; 424/486; 424/DIG. 14

[58] **Field of Search** ..... 602/77; 604/48, 604/500, 514, 515, 518, 346; 514/931, 932, 933, 934, 967; 424/195.1, 486, DIG. 14

[56] **References Cited**

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5,840,771 11/1998 Oldham et al. 424/195.1

Primary Examiner—Nathan M. Nutter

Attorney, Agent, or Firm—Vorys, Sater, Seymour and Pease LLP

[57] **ABSTRACT**

In order to prevent conception and/or the spread of sexually transmitted diseases (STD's) one or more lectins capable of binding sperm and/or the pathogenic microorganisms responsible for STD's are administered to the vagina prior to sexual intercourse. The lectins immobilize the sperm to render them incapable of fertilization and also bind to the microorganisms to render them non-pathogenic or to the cells to prevent infection by the microorganisms. Lectins can also be administered to treat sexually transmitted vaginal infections. The invention also encompasses a device for to be placed in the vault of the vagina which comprises a ring which surrounds the cervix and a membrane spanning the central aperture of the ring to prevent the direct contact of ejaculate with the cervical tissues. The device is impregnated or coated with lectins and releases them into the vaginal environment over a period of time.

21 Claims, 2 Drawing Sheets

DOCUMENT-IDENTIFIER: US 3773929 A
TITLE: PHARMACEUTICAL COMPOSITIONS COMPRISING ORGOTEIN AND THEIR USE

OCR Scanned Text (8):
3,773)929 15 linked dextran, is preferred. Resin cbromatography is most preferred for reasons of production economy and because larger amounts of protein can be processed at one time. An albumin removal step is essential, when the protein source contains albumin, because the other isolation steps usually employed in a process for producing the desired protein product increase rather than decrease the absolute albumin content of the purified protein. For example, the albumin content of the total soluble protein fraction from bovine liver is 7.5%; bovine kidney, 8%-, from porcine kidney, 10%; from bovine spleen, oysters and mussels, 2-3 %. In the fractionation steps described hereinafter, albumin content of the concentrates rises to 22-3 1 %. Gel electrophoresis or resin chromatography is effective in reducing the albumin content of these concentrates to below I %. Thus, concentration without electrophoresis or resin chromatography of a protein source containing significant amounts of albumin causes a build-up of albumin which precludes iis safe use as an injectable pharmaceutical agent and prevents it from manifesting useful pharmacological activity. Free-falling curtain electrophoresis is capable of removingmuch of this albumin. Gel electrophoresis and resin chromatography remove even moreAn albumin removal step is not, of course, required when albumin-free starting material, such as red blood cells from many species, is used. A commercially available electrophoresis unit which can be used for free-falling curtain electrophoresis is the Brinkmann -Model FF. The separating chamber in one such unit for instance is 50 centimeters square and 0.5 to I mm. in depth. The temperature is maintained as close to 5o C. as possible. The unit permits the collection of up to 48 fractions. In operation, the protein, dissolved in trismaleate-Me++ buffer, pH 7.6, is applied continuously. Currents of about 1,000 volts and 20-20 ma. are used. With properly pre-purified protein mixtures, the desired protein chelate will be found in fractions 10-26 which are pooled, dialyzed and lyophilized. The construction and the operating characteristic of this unit limit its r-apacity to about 500 mg. runs. The isolated protein is obtained in batches of about 100 mgs. which are subsequently pooled. Using this method, albumin levels can be lowered to about 5-10%. However, levels below 5% are not ordinarily achieved. 91 A more effective purification technique is the gel or zone" electrophoretic purification described herein which uses a gel supporting medium, e.g., polyacrylamide, agarose, starch, etc. Substantially complete removal of albumin and other extraneous proteins can be achieved by this technique, by virtue of their different speeds of migration. The preferred preparative gel electrophoresis media is polyacrylamide (5 to 10%). Cellulose, cross-linked dextran (Sephadex, Pharmacia, Upsala, Sweden) and starch modifications (ethanolized, etc.), agar, sucroseagar and other agar modifications are satisfactory but have the disadvantage of their gels being more fragile. For a description of the principles of gel or "zone" electrophoresis, see '@Gel Electrophoresis," J. F. Friedrick, Editor, Annals N.Y. Academy Sci., 121, 305-650 (1964). A production model developed for disc gel electrophoresis purification has a 5 to 7% polyacrylamide block 32 centimeters long, 10 centimeters wide and one centimeter deep held between jacketed top and bottom plates made from clear plastic. The dimensions of the block are such that cooling is very efficient and the small depth ;@ssures rapid temperature equilibrium between center and surfaces. Cooling is provided by a refrigerated circulating system employng ethylene glycol-water. Operation is carried out at 600-1000 volts and 200-500 ma. These currents together with the very efficient cooling make it possible to handle 1-5 g. quantities of starting protein during a developing process of 2-10 hours. The material is ap- 16 pled to a starting trough as a highly concentrated solution in tris-maleate-Me++ or similar buffer at pH 7.4. At appropriate times of development, buffer is passed through the gel at right angles to the direction of electro- phoretic flow to elute the protein. Location of protein bands, completeness of elution and protein concentration in eluted fractions are determined by spectroscopy at 280mu or by staining of indicator sections. In gel electrophoresis, beef liver orgotein is found be- 10 tween slow-moving, gamma globulin protein type fractions and the fast-moving, albumin-type protein fractions. Another preferred means for removing albumin and other types of extraneous

proteins remaining after the previously described fractionation steps is by chroma- 15 tography, e.g., using as chromatographing media "porous" resins which "Mter" proteins according to molecular volume, i.e., act as molecular sieves. One such resin is Sephadex (Pharmacia, Upsala, Sweden) a cross-linked dextran resin of defined pore size. The partially purified 20 orgotein protein in a buffer-Me++ solution, is deposited in highly concentrated form on a column of the resin and then eluted in the manner conventional for chromatographic columns, but using a buffer solution containing a divalent metal of ionic radius of 0.60 to 1.00 A, prefer- 25 ably 0.65 to 0.79 A, e.g., magnesium, or a mixture of two or more of magnesium, copper and zinc, as eluting solvent. -Ionic strength variations often facilitate separation and subsequent elution. In the application of W. Huber, S.N. 815,175, filed Apr. 30 10, 1969, abandoned in favor of S.N. 31,791, filed Api. 24, 1970, now U.S. 3,579,495, there is disclosed a process for isolating orgotein from red blood cells. According to that process, the red cells are separated from the plasma of the blood by centrifuging. Repeated washing of the 35 separated cells with isotonic solvenis and re-centrifuging removes residual plasma and with it the plasma albumin, adhering to the compacted cells. The plasma-free red cells are then ruptured by hemolysis, using conventional procedures. See M. Moskowitz and M. Calvin, EXP. Cell 40 Res., 3, 33 (1952); S. S. Bernstein et al., J. Biol. Chem., 122, 507 (1938). Hemolysis %iith deionized water and sonification at 0-5' C. is preferred. The hemoglobin and stroma are separated froni the lysed mixture by methods known 'M the art. Se6 E. R. 45 Waygood, Methods in Enzymology, vol. 2, 836 (1955), Academic Press. Preferably, for hemoglobin this is accomplished by adding a halogenated aliphatic solvent which apparently forms an insoluble complex with the hemoglobin, along with a water-misdible organic solvent to bring a small proportion of the immiscible solvent into 50 the aqueous phase. Hemoglobin complex and stroma then can be removed by centrifugation. The supernatant, n6w substantially free of hemogl obin and stroma, is then freed of carbonic anhydrase, and other 55 enzymes by heating the supernatant in the manner described in S.N. 815,175 and Example 4 herein, until the carbonic anhydrase has been- inactivated by heating, i.e., 10-30 minutes at 60-70' C. Thereafter the mixture is immediately cooled to well below room temperature. The 60 precipitated proteins are removed by filtration or centrifugation. The supematant remaming after removal of the precipitated proteins contains the orgotein protein as the, or one of the, predominant proteins. After removal of the precipitate formed in the heating step, the orgotein 65 protein in the resulting solution, or isolated therefrom by dialysis and lyophilization, @an be purified and isolated by mixed bed resin filtration, electrophoresis and/or g filtration through a polymer which acts as a molecular 70 sieve, as described herein. For literature methods for isolating orgotein, see the references cited above. These liroducts, after@ processing as described above to provide sterility, non- pyrogenicity and stability, can be employed in the composition of@this 7r, invention.

OCR Scanned Text (9):

31773,929 17 Pharmacodynamic properties of orgotein Pharmacological and clinical data have established orgotein is useful in the treatment of a variety of ailments and diseases in animals, particularly those which result in inflammatory and related stress conditions manifest- 5 ing themselves in the afflicted animal. This utility has shown no specificity as to any particular species of mam- mal to date. The action of the orgotein is fast and effec- tive. For example, orgotein in man and horses is useful 10 in relieving the pain, tendemess and disfunction follow- ing acute traumatic injuries and in the treatment of ortho- pedic disfunction, e.g., bony exostosis. It is effective in combating the effects and sequelae of shock and toxic conditions. Orgotein also is effective in certain viral dis- 15 eases, e.g., human influena A and B, viral horse pneu- morhinitis, canine distemper, picoma virus induced feline pneumotracheitis, and disfunctions based on the family of herpes virus. The animal, toxicology of orgotein has been extensively studied and found to be largely unevent- 20 ful, demoiistrating its lac,k of toxicity. Orgotein has been studied exten,sively in various animal models of induced inflammation, viz., foot paw edema in the rat produced by carrageenin, or ye4st, or silver nitrate; adjuvant-in- duced polyarthritis in the rat; passive cutaneous Arthus 25 reaction; cotfon pellet granuloma in the non-adrenalec- tonized and bi-laterally a&enalectonized rat; pox-virus- inducod skin edema 'm the rabbit; PVA sponge impiant- induced inflammation and wound healing and antiserum- indiiced skin edema and

active anaphylaxis in the guinea 30 pig and the mouse. Potent beneficial effects of orgotein were observed in all these models. For biological stand- ardization and quality control the assay based on anti-serum-induced skin edema has been used. In guinea pigs, using this antiserum-induced inflamm' 35 tion according to the method of Ungar et al., Arch. Int. Pharmacodynam. 123, 71 (1959), a highly purified sam- ple of the protein has an inflammatory inhibiting activ- ity of about 50% at a level of 1.0 mg./kg., which is the same order of activity as produced by about 60 mg./kg. 40 of butazolidine and about 20 mg./kg. of prednisolone. Thus, by this test, orgotein has higher potency than two of the standard non-steroidal and steroidal anti-inflam- matory agents. Orgotein is effective in treating a wide variety of in- 45 flammatory conditions, including those in which synthetic anti-inflammatory agents have limited utility, e.g. because of toxic side effects upon prolonged use. More specifically, orgotein is efricacious in ameliorating in,flammatory conditions and mitigating the effects thereof, 50 for instance those involving the urinary tract and the joints, in various mammals. It is useful in alleviating the symptoms of and the structural deformities associated with post-traumatic arthritis, and rheumatoid diseases, such as bursitis, tendonitis, osteoarthritis, non-surgical disc syn- 55 drome known as ossifying pacchymeningitis in dogs (spondylitis) and myositis. Diseases of the genito-urinary tract which respond to orgotein treatment include both acute and chronic iiiflammatory conditions, e.g., epidi- dymitis, urethro-trigonitis, intersititial cystitis, radiation 60 cystitis, urethral stricture, chronic congestive prostattis and naphritis with impared kidney function. Orgotein can alle- viate uremia and the anemic sequelae, e.g., in cats with cystitis and human patients with uremia and anemia. Orgotein also has utility in the treatment of diseases 651 involving an imbalance of the auto-immune system, alone and in combination with drugs conventionafly used to treat such diseases. Typical are the "collagen" type diseases, e.g., rheumatoid arthritis, lupus erythematosis and sclero- derma, allergic states, e.g., penicillin reaction, which are 7o characterized by multiple wheals, indurations, erythemas, edema or itching, and drug-induced, e.g., demeclocylin hydrochloride photosen@itization. States of thock can@ be reversed by orgotein, e.g., those induced by curard-like drugs, overwhelming sepsis, drug 75 18 toxicity, carbon monoxide, surgical and traumatic shock, anaphylaxis, etc. even though it does not possess significant CNS stimulant activity. @In animal pharmacology, orgotein has been shown to be eilective in a number of standard models of induced inflammation, thus predicting the anti-inflammatory effects observed clinically in man and animals. In the guinea pig skin edema model, when given concomitantly with synthetic anti-inffammatory agents, e.g., prednisolone, dexamethasone and phenylbutazone, orgotein potentiates the suppression of inflammation, thus indicating its use in- combination therapy. Since orgotein does not inhibit wound healing and is not immunosuppressive, its substitution for some or all of the anti-inflammatory steroids in antiinflammatory therapy is especially desirable. In addition to its broad-based anti-inflammatory effects, orgotein protects from shock reactions produced upon antigenic challenge after prior- sensitization. This inhibition of immediate hypersensitivty was also demonstrated in Arthus reaction. These observations established a strong rationale for clinical evaluation of orgotein efficacy in various diseases with allergic manifestations, e.g., asthma, particularly since orgotein does not interfere in delayed hypersensitivity- reactions, i.e., is not expected to activate disease processes held in check by cellular-immune phenomena. Orgotein also has been found to be effective in various in vivo models of virus diseases. In vitro, orgotein was found to be effective against the canine distemper virus, feline picorna virus and human herpes simplex virus. Whether the in vivo antiviral effect of org(>tein is on viral proliferation or on inflammatory and/or immunological sequelae of virus infection has not been determined. The action mechanism of orgotein appears to involve the sequelae of immune-related events. Orgotein at 10-5 M or less exhibits a pronounced chemotactic effect on PMN'S, both in vitro and in vivo, and in vitro inhibits- complement per se as well as complement fiaxation in guinea pig, rabbit and human sera. Immune event-related mechanisms thus may be responsible for the efficacy of orgotein as an anti- inflammatory, anti-shock and anti-viral agent. Membrane stabilization effects of orgotein could augment its other effects and contribute to the overall efficacy observed clinically. The action mechanism of orgotein, at least in Part, is different from that of both anti-histaminic drugs and corticosteroids. The safety aspects of orgotein have been exhaustively explored with acute, subacute, and chronic toxicology studies in various animal species, including reproduction and teratology

studies.,Intravenous, intramuscular vaginal and intraurethral routes of administration have been used. - Sensitization aspects also have been thoroughly explored using intradermal and intraperitoneal sensitization routes with intradermal and intravenous challenge routes. No undesirable effects have been seen in any of these studies or in any of the clinical studies in animals and man conducted to date. In vivo, the minimal lethal dose in animals was not attained at doses over 2500 times @the anticipated average clinical dose in humans on a weight basis. Veterinary clinical studies with orgotein have been conducted in orthopedic disorders in horses, in urethr6cystitis in cats and in canine distemper. The horse study demonstrated clear-ciit drug efficacy in over 75% of the tre I ated animals. In a double-blind, controlled cat cystitis study, interim evaluation of 21 orgotein and 22 placebo cases indir-ated a pronounced benefit of orgotein administration, statistically significant at the 0.01 level. In a controlled canine distemper study, a preliminary analysis indicated an enhancement of surivival probabilities in the orgotein recipients. Clinical human investigations have shown orgotein to be effective in the treatment of arthritides. Preliminary clinical evidence indicates at least symptomatic relief in progressive systemic sclerosis. Clinical evaluation of orgotein in urological diseases have shown pronounced efficacy

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21 Tablet ,s cont4in the orgotein ingredient in admixture with nontoxic pbarmacuticallv acceptable excipients which are suitable for inanufacture of tablets. These excipients may r be, fo exampl(,, inert diluents, f.or example calcium carb6nate, sodium..ca,rbonate, lactose, calcium phosphate or sodium phosphate . ; granulating and disintegratiing agents, for ex@tmple maize.starch, or alginic acid; binding agents, for. example starch gelatine oi acacia, and lubricating agents, for examp@,e magnesium stearate, stearic acid or iale. The tablets ffiay be uncoated, but preferably are coated by known te,chniques to delay disintegration and abso@ption iii th6 gastro-intestinal tract and to protect the orgotein from stomach acids. Formulations for oral use may also be in the form of hard gelatine. capsi#es wherein the orgotein is mixed with an @inert, solid dfluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with an oil medium, for example arachis oil, liquid paraffin or olive oil. Aqueous soluti6ns contain the orgotein in admixture with excipients suitable for the manufacture of stable aqueous solutions, e.g., NaCl, to provide a saline or isotonic solution, buff,er agents, acids or bases, etc. The aqueous solution can also contain one or more preservafives, for example ethyl or n-propyl p-hydroxybenzoate. @.0i,ly suspensi6ns may be formulated by suspending orgotein in an oil suitable for injection, topical or oral administration,,in a vegetable oil, e.g., arachis oil, olive oil, sesame. oil or coconut oil, or in a mineral oil, e.g., a. liquid p4raffin. The oily suspensions may contain a thickening -agent, for example beeswax, hard paraffin or cei@i alcoh6l. These compositions may be preserved by the addition of an antioxidant, e.g., ascorbic acid. The pharmaceutical compositions of the invention can be in the form of oil-in-water emulsions suitable for oral or, parenteral administration. The oily phase may be a vegetable oil, e.g., olive oil or arachis oils, or a mineral 94, e.g., l@quid paraffin br mixtures of these. Suitable emulsifying agents are naturally occurring gums, e.g., gum acacia or gum tragar-anth, naturally occurring phosphatides, e.g., soya bean lecithin and esters of partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleatei and condensation products of the said parti.al, esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. I The compositions of this invention can also be in the form of an aerosol,for inhalation or topical administration slow-dissol-ving pellets for implantation. The compositions of this invention can be administered parenterally, orally and topically. The term parenteral as used herein includes subcutaneous, intradermal, intravenous, intramuscular, intraocular, intrastroma, intrasynovial,- intrathecal, intramural, intraarticular, intraperitoiaeal, intrascrotal, intraosseous, intraspinal, intraligamentous =d intrasternal. Intramuscular and subcutaneous@administration is usually preferred except when thd orgotein is administered proximate a localized area of iifflammaiion. . . : The @ pharinaceuti6al compositions can be in the form of a sterile. injectable preparation, for example, as a sterile injectable aqueous solution. The solution can be fonnulated according to the known art using those carriers mention6d, abo@e. The sterile injectable preparation can Also be a sterile injectable solution or suspension in a nontoxic pareiiternally

accept6ible diluent or solvent, e.g., 1,3butanediol. @ The.compositions of this invention can be in the form Of @uppositories -for vaginal and rectal administration. These'comositions can be;prepared by mixihg 6rk6teiri v@ith a suit@bl@ nonii-ritating excipient which is solid at ordinary temperaitires but liquid @ at the rectal temperature and *ill therefore inelt in the@reciiiin to release the drug. Such materials are cocoa-butter and polyethylene glycols. -The-66inp6sition@ of thi invehiion combine an effective ui@dt do@age aniouni.:of orgotein, i.e., the orgotein is pres- 8,773)929 22 ent at a concentration effective to evoke the desired response when a unit dose 6f the composition is administered by the route appropriate for the particular pharmaceutical carrier. For example, liquid compositions, both topical and injectable usually cdntain about 0.5 to 20 mg. of orgotein per 6.25 to 10 cc., preferably about 0.5 to 5 cc., except I.V. infusion solutions, which can also be more dilute, e.g., 0.5 to 20 mg. orgotein per 50-1,000 ml., preferably 100-500 ml. of infusion solution. Tablets, 10 capsules and suppositories usually contain 0.1 to 25 mg., prefera-bly I to 10 mg., per unit. The weight ratio of orgotein to liquified propellant in an aerosol for topical or inhalation, administration can be quite high, e.g., 0.5-5%. Topical -compositions usually 15 contain orgotein in a concentration of 0.1 to 1% in aqueous solution or non- aqueous suspension. The amount of orgotein administered is dependent on several factors, including the species of patient, the conditioii of the patient prior to orgotein therapy, the par- 20 ticular disease and its progression and the route of- administration. The usual individual parenteral dose range of orgotein is about 0.5 mg. to 20 mg., usually I mg. to 5 mg. The dose is not significantly dependent on the weight of the patient. For example, within a dosage 25 regimen in animals, a usual single dose for a cat (0.5-20 lbs.) is about I mg.; for a dog (5-50 lbs.) 2 mg.; and for a horse (1,000 lbs.) 5 mg. Rather, the size of an individual dose is more dependent upon the dynamics of the disease pattern. For instance, with a severe infection, e.g., 30 with associated toxemia or uremia, injections spaced about every six hours are required, with the frequency subsecluently reduced to 8-12 hours and then every 24 hours or longer, depending on the clinical picture. Tbus, during the acute state of a disease, the frequency of the injections 35 is often more critical than the amount of each individual dose. Larger individual doses are usually administered when orgotein is administered orally, e.g., 5 mg.- 25, 50 or 100 mg., or even more. Sirnilarly, wheii a solution or suspen- 40 sion of orgotein is applied topically to the skin or infused into the bladder, vagina, large intestine, etc., the total amount of orgotein administered in single uninterrupted dosing can vary from 5 to 100 mg. or more. Con- versely, when orgotein is administered into the resp ry 45 tract, e.g., in the treatment of asthma, anaphylactic or other acute shock conditions, e.g., as a spray, mist, aerosol, etc., lesser amounts, e.g., 5 to 0.5 mg. or less, are sometimes indicated. The spacing of the individual doses is also partially 50 determined by the nature of the ailment. In treatment of inflammatory syndromes, orgotein is usually administered in multiple-successive dosages, spaced as frequently as 6-12 hours apart and as long as six weeks apart. Usually, daily doses are administered until symptomatic relief, e.g., .55 from pain and stiffness, is obtained. Thereafter, doses are spaced further apart, the frequency being adjusted so that recurrence of symptoms is avoided and relief maintained. Treatment can be continued over a period of several weeks or months, and indefinitely for advanced r)o chronic cases. In treating viral infections, orgotein is usually admin7. istered in multiple successive dosages, spaced as frequently as every six hours. Usually, doses every 6 to 12 hours are administered until symptomatic relief, e.g., from 65 pain and fever, is obtain6d from the viral infection. Thereafter, doses spaced I to several days apart are admin- istered until all symptoms of viral in tion are gone. Treatment is continued until aR symptoms and signs are gone. A subsequent booster shot or two may be given 70 after 'several days. The number of successively spaced d6ses of orgotein necessary in order to alleviate at least some of the symptoms associated with the viral infection will vary widely, depending on the nature and status of the infection. In some cases, cenical relief is obtained 75 in a period of a few bours. Others require longer periods

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3;773,929 23 of therapy of from several days up to several weeks. Because symptomatic relief sometimes precedes complete elimination of the viral infection, care must be taken not to terminate orgotein therapy prematurely. Orgotein usually is administered by installation or by injection, e.g.,

intramuscularly, subcutaneously, intravenously or intradermally. I.M. is preferred, except in case of shock where I.V. is sometimes preferred for more rapid onset of effect, and in certain localized disorders, e.g.,, radiation and interstitial cystitis, where local injection is often more effective. Individual doses usually fall within the range of 0.5 to 20 mg. The preferred range for humans is about 0.5 to 4 mg.; for horses, about 5.010.0 mg. The exact dosage is not critical and depends on the type and the severity of the disease. roral administration is possible if the protein is protected from the destructive action of the acid pH and enzymes of the stomach, e.g., in the form of an enteric coated tablet, although much larger doses are required by this route. The protein has topical activity, e.g., when applied as a solution, aerosol, cream, ointment, salve, etc., which renders it useful for treating corneal and conjuctival, respiratory, genito-urinary and dermatological disorders. Desirably, it is administered with a surfactant and/or penetrant to ensure better contact and penetration. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, tO be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. PREPARATION I The following is a general procedure for isolating proteins from natural sources thereof to provide a suitable starting proteinaceous material for the process of this invention. Mechanically remove as much extraneous material as possible from a freshly harvested, washed and cleaned plant or animal source of protein. In the case of animal tissue, glands and organs, remove fat, connective tissue and blood vessels. Conduct all subsequent steps below 5 o C., except as indicated. (a) Toluene method Homogenize the protein source and immediately add 3 vol. of deionized water or a suitable buffer, 0.05-0.30 M, e.g., maleate, phosphate,- tris-maleate, barbital, trishydroxymethyl-aminomethane, borate, eacodylate, glycinesodium hydroxide, etc., containing IXIO-4 to 2XIO-1 M of a water soluble salt, e.g., chloride, sulfate, phosphate, acetate, citrate, maleate, borate or phosphate, etc. of a physiologically essential divalent metal, e.g., calcium, Cobalt, copper, iron, magnesium, manganese or zinc. Adjust to pH 7.0-7.8. Stir the resulting mixture for several hours. Then add slowly 0.01 vol.-equivalent of toluene and continue stirring for several more hours. Let sit until the supernatant is reasonalbly clear. Filter, e.g., through cloth, cotton, glass wool or filter-aid, or centrifuge. Exclude direct light in these operations. Immediately freeze the filtrate and lyophilize it. If direct lyophilization proves difficult, dialyze first against 0.001 M buffer containing 0.1- 5XIO-4 M bivalent metal salt, e.g., Ca++, Co++, Cu++, Fe++, Mg++, Mn++, Zn++. The resulting powder can be stored in the cold, preferably, at below O' C. (b) Ac6tone powder method Suspend finely disintegrated whole tissue in any of the: buffer,-Me++ mixtures of (a) above, bring to pH 7.0-7.8 and cool the dispersion to 0". Add to the dispersion very slowly 10 vols. of acetone at -10' C. with rapid mechanical stirring. Let settle for about 10 minutes, and decant the supematant aqueous acetone. Collect the- precipitate either by centrifuging or by vacuum filtration through 24 a No. I Whatman paper on a wide Buchner funnel in a cold room at O'. Wash the precipitat6 twice by suspending on each occasion in about 3 vol. (calculated from the original volume of dispersion) of acetone at -101 C. Re- move the acetone from the precipitate, first using a stream of nitrogen followed by drying the powder in vacuo over H2SO4. The last acetone treatment can be followed by washing with dry peroxide-free diethyl ether (at -15'), which greatly facilitates rapid drying. Store the dried 10 material in the cold, preferably in vacuo over a drying agent. Alternatively, disintegrate the whole tissue directly in 10 vol. of acetone at @-15' in a Waring Blendor (for 3 minutes), and retreat the precipitate with acetone as 15 described above. If the first acetone precipitate contains much lipid material, washing it with n- butanol at -15' greatly improves the subsequent extractions. Alternatively, cut 1 kg. of fresh bovine liver, free firom 20 connective tissue, into five or six pieces, rinse with tap water and mince. Homogenize portions of mince (200 g.) in a Waring Blendor with 200 ml. cold iso- osmotic KCI solution for 20 sec. Immediately mix the bomogenate in the blender with 200 ml. of acetone at -10' for another 25 20 sec. Pour the acetone-treated hemogenate with stirring into a 10 liter beaker containing 2.5 liters of acetone at -10'. When the final portion of mince has been treated, add to the contents of the beaker cold acetone to a volume of 10 liters and mix. Hold at 4' for a few minutes. Decant 30 the clear supernatant and again mix the contents of the beaker with acetone to 10 liters. Decant the clear supernatant and filter the suspension rapidly on a Buchner funnel covered with a sheet

to exclude as much air as possible. Before the cake on the funnel is completely dry, wash 35 with 2 liters of cold acetone. Continue the filtration until the particles are completely dry. Break up the solid material, spread out on filter paper and air-dry, preferably under a cover of nitrogen. Finely grind the powder wh.Ue cold and store in vacuo 40 at 4'. The yield is about 250 g. of powder. PREPARATION 2 The following is a general procedure for producing and isolating orgotein from protein sources of the type pro- 45 duced in the above-described Preparation 1. AR operations are carried out in 0.1 M tris-maleateMe++ buffer at pH 7.4, unless otherwise indicated. 0.05 M to 0.2 M tris-phosphate-Me++, tris-succinate-Me++, tris-glycine-Me++ and tris-HCI-Me++ buffers work equally .50 well. All operations involving organic solvents are carried out at 0 to 2' C., or lower using organic solvents precooled to -10' C. All other operations are at temperatures below +5' C., except as indicated. 55 (A) Removal of buffer-insoluble material In the cold and in the absence of direct light, stirr 100 g. of dry powder, obtained.'according to Preparation 1, into one liter of- tris-male@te buffer. After several minutes add 6.5 g. MgSO47H20 in portions and adjust pH to 7.4 with I N sodium hydroxide. Then add an additional 600 60 ml. of tris-maleate buffer and an additional 6.5 g. MgSO47H20 Re-adjust to pH 7.4. Then add an additional 400 ml. water and continue stirring in cold room until about 6 65 hours have elapsed from the start of the operation. Let the mixture settle and then filter or centrifuge. Adjust the Mtrate to pH 7.8, hold in the cold until precipitation is complete, centrifuge and filter supernatant. For storage, lyophilize the filtrate as described in the preparation. 70 With some raw materials, e.g., liver, the above step and the antecedent . Preparation 1 preferably is carried out with 0.1 M manganese sulfate providing the bivalent metal. Transchelation, i.,e., removal of most manganese and replacement by magnesium, is achieved using tris- 75 maleate-magnesium salt buffer in a subsequent step. In

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3,773)929 39 the horse developed symptoms of colic, he was exercised, ridden on the track and played polo. Subsequent autopsy verified the existence of previous massive coronary throm- boses. EXAMPLE 17 5 Three horses with acute flexor deep and superficial tendonitis were given 5 mg. orgotein intramuscularly daily. Within 24 hours there was a definite reduction in lameness and tenderness on pressure to the affected area. 10 EXAMPLE 18 'Ibree dachshund dogs with ossifying pacchymeningitis (non-surgical disc syndrome) and paralysis of the hind quarters were improved after 3 to 5 days following daily 15 intramuscular injections of 2 mg. orgotein, and in eacli case remained clinically well for over nine months to one year without further treatment. EXAMPLE 19 A Siamese spayed female, age 12 years, suffering from 20 panleukopenia and clinically moribund was brought back to life, given orgotein at 2 mg. every 6 hours for 2 days. This same animal developed another attack over a year later and responded to the same treatment. 25 EXAMPLE 20 TOPICAL USE (a) For installation in an inflammed bladder, e.g., cys- titis the urine is drained using a small soft rubber - catheter. 5 ml. of a solution of orgotein in 0.9 % saline at a concen- tration of 3-4 mg./ml. and is then instilled into the 30 bladder. A small amount of air is injected to clear the catheter and the catheter is then withdrawn. The orgotein solution is not rapidly expelled. Clinical benefit, which may last six weeks, may be noted within an hour. I (b) Orgotein (10 mg. lyopholized powder) is incorpo- 35 rated into and mixed (1-10 mg./g.) with an oil and water emulsion base, e.g., HEB (Haydens Emulsified Base) con- taining acetyl and sterol alcohol, petrolatum, liquid petro- latum, sodium lauryl sulfate, propyl glycerol, butyl and 40 methyl paraben and water. Topical application of this mix- ture to a freshly abraded skin surface or on to a hemor- ' rhoid effectively and quickly reduced inflammation, pain and swelling. Topical use thereof on inflamed mucous membranes, eye, mouth, anus, genital tract and sinuses.in 45 an appropriate liquid pharmaceutically acceptable carrier reduces inflammation and relieves accompanying discom- fort. Altematively, a 0.1-1% solution of orgotein in a buf- fered isotonic solution can be used, alone or in combina- tion witli a thickening agent, e.g., 0.02% polysorbate 80, 50 or PEG 4,000, an antibiotic, e.g., neomycin sulfate or tet- racycline and/or an antiinflammatory steroid, e.g., dexa- methasone or betamethasone, and optionally, a decongest- ant for nose drops, e.g., phenylephrine hydrochloride, or a vasoconstrictor for eye drops, e.g., tetrahydrozoline hydro- 55 chloride. EXAMPLE 21 65 cases of hydrocoele were treated by aspiration and 60 injection locally into the hydrocoele sac of 4 mg. -

orgotein. The treatment was effective, as measured by no or less rapid refill time, in most of the patients. EXAMPLE 22 65 24 cases of chronic congestive prostatitis were treated with 3 mg. orgotein intramuscularly with definite improve- ment of their inflammatory problem repeated in 2-6 months, when necessary. EXAMPLE 23 70 3 cases of urethro trigonitis in the female were treated with marked benefit with 3 mg. intramuscular injections of orgotein 2-3 times a week for 1-2 wecks, repeating in 2-6 mgnths if necessary. 75 40 EXAMPLE 24 Human joints, hips, knees and shoulders of patients suffering from arthritides have been improved by intraarticular injection of 2 mg. orgotein in about I ml. of previously removed synovial fluid or saline solution. EXAMPLE 25 19 patients with radiation cystitis who had been treated with all known methods with no avail, were treated by multiple intramural injections through a cystoscope of a total of 10 mg. of orgotein in 10 ml. isotonic saline solution. The treatment was repeated 3 times a week for 1-2 weeks and thereafter in 2-6 months, ff needed. All patients demonstrated a marked improvement. 5 cases of interstitial cystitis in which all previous treatment failed, showed marked improvement with similar orgotein therapy (intramural). EXAMPLE 26 Human patients with herpes simplex of the mucous membranes (oral, genital and conjunctival) were successfully treated by orogtein 2 mg. intramuscular injections 2 times daily for 1-2 days and then daily for a total of 6-7 days. Cases of corneal and ophthalmic herpes were successfully treated with orgotein following the same protocol after all other treatment faiied. Mononucleosis successfully treated with 2 mg. of orgotein intramuscularly daily for 3 days. EXAMPLE 27 The trauma and lameness ass(>ciated with sprains is relieved more rapidly by the injection of 2 mg. of orgotein directly into the tendon sheath. EXAMPLE 28 A patient with anemia, renal failure and diabetic gangrene who had been severely diabetic for 40 years and had previously been given 45 blood transfusions was given orgotein intramuscularly (2 mg. daily for 10 days, increasing to 4 mg. daily for 4 days, then resting 3 days). During orgotein therapy, transfusions were not required for over sixteen months. The uremic and anemic problems are controlled and insulin requirements have been halved. EXAMPLE 29 A patient suffering from pernio (frostbite), with inflammation, impaired circulation of the extremity and thrombosis of the small blood vessels, was given 2 mg. of orgotein intramuscularly daily for 3 days, followed one week later by the same dosage. Marked improvement was noted. The procedure of Examples 10 to 19, 22, 23, 26, 28 and 29 can be followed with at least as good results by the administration of the orgotein subcutaneously. The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples. , From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. What is claimed is: 1. A method of treating an inflammatory condition which comprises the administration of a therapeutically effective amount of a pharmaceutical composition comprising, in admixture with a pharmaceutically acceptable carrier and substantially free from other proteins with which the orgotein was admixed or associated in the source thereof, an effective unit dosage amount of orgotein, a member of a family of protein congeners characterized physically by being the isolated, substantially pure form of a globular, buffer and water-soluble metalloprotein having a highiy compact native conformation